CURRICULUM VITAE

Personal informations

Dr Gaëtan L.A. MISLIN
Born 20th December 1971 in Mulhouse (France), 52 years old
Married, two children
French

Professional informations

CNRS Research Director (ORCID 0000-0002-5646-3392)

Co-Head of team Metals and Microorganisms: Biology, Chemistry and Applications (MMBCA)

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Education and professional cursus

1996-1998	:	PhD in Organic Chemistry (LCOS, Univ. Strasbourg, Dr. Michel Miesch)
1999-2001	:	Research Assistant (Postdoc, Louvain-la-Neuve, Belgium, Pr. Léon Ghosez)
2001	:	CNRS Research Officer
2006	:	Habilitation (Univ. Strasbourg)
2017	:	Co-Head of team MMBCA
2019	:	CNRS Research Director

Scientific production

1 book translation (Engl. to Fr.). The Organic Chemistry of Biological Pathways (Eds Roberts and Co. Publishers, Authors: J. McMurry et T. Begley) was translated into *Chimie Organique des Processus Biologiques* (Eds De Boeck Université, Belgium).

2 patent applications as principal inventor

Preparation of bis-hydroxyphenyl-thiazole-4-carboxamide derivatives as cytoprotectants against iron overload and antiproliferative agents. **Mislin, G.L.A.**; Schalk, I.J.L.; Lescoat, G.J.-M.; Gaboriau; F.R.; Rodriguez-Lucena, D. *PCT Int. Appl*. (2009) WO 2009053628.
Gold(I)-phosphine 1,2,3-triazole derivatives with antibiotic properties. **Mislin, G.L.A.**; Schalk, I.J.L.; Plésiat, P.; Paulen, A. (WO2019243273).

61 peer reviewed articles

- **20** as corresponding author
- **15** result of an international collaboration
- **5** as first first author

Teaching and scientific supervision

6 PhD (4 defended, 1 ongoing, 1 abandoned)
6 postdoc fellows
1 CNRS Engineer
10 Master students
6 Engineer trainees

Course of Organic and Bioorganic Chemistry (School of Biotechnological Engineering-ESBS, Illkirch (32 hours/year, 2014-2020).

Awards

2012 Scientific Excellence Reward (PES, CNRS)
2018 Teaching and Research Reward (PEDR, CNRS)
2022 Research Prize (Force Foundation)

Grants (2016-2024)

Maturation fund TTO Conectus (2016-2020, coordinator)	:	370 k€
ANR (project VECTRIUM, 2019-2023, coordinator)	:	220 k€
Foundation for Research in Chemistry (2021, partner)	:	12 k€
French association againstcystic fibrosis(2022-2023, partner)	:	8 k€
Force Foundation (2022-2024, coordinator)	:	150 k€
French association againstcystic fibrosis(2024-2025, coordinator)	:	33 k€
ANR (project RHEINGOLD, 2025-2027, coordinator)	:	220 k€

Current projects

Resistance to antibiotics will be a major threat for mankind in the forthcoming decades. The raise of increasingly antibiotic-resistant strains is the result of a lack of massive innovation in anti-infective discovery over the 40 last years. The discovery of new antibacterial strategies is therefore urgently needed to regain control on resistant pathogens. This aspect is particularly critical for infections involving Gram-negative bacteria. Indeed, these pathogens are naturally resistant to many antibiotic families due to the low permeability of the outer membrane. iron uptake systems are gates in this barrier and could be used to introduce antibiotics in a so-called Trojan horse strategy. Siderophores excreted by bacteria to fulfils their needs in this essential and ubiquitous nutrient, are able to chelate iron(III) and promote the uptake via dedicated specific transmembrane acquisition systems. An antibiotic conjugated to a

siderophore vector (sideromycines) is much more efficiently assimilated. Using this strategy, the activity of the vectorized antibiotic is significantly increased (up to 1000x) and antibiotics usually inactive against Gram-negative bacteria can present a spectacular spectrum broadening **(1)**.

The multidisciplinary team "Metals and Microorganisms: Biology, Chemistry and Applications" (MMBCA) co-directed by Dr. Isabelle Schalk and Dr. Gaëtan Mislin, studies since nearly two decades the siderophore-dependent iron uptake systems on *Pseudomonas aeruginosa*, a critical pathogen responsible for severe infections. This team is now about the five most cited in the field. Using purified siderophores and molecular tools (siderophore analogues, deuterio- or fluorescently labelled, etc.) synthesized by chemists supervised by Dr. Mislin, biologists of the team elucidate, to a structural and functional point of view, the uptake pathways of endogenous siderophores of *P. aeruginosa* (pyoverdine, pyochelin). In the last ten years these investigations were extended to exogenous siderophores used by *P. aeruginosa* (enterobactin, ferrichrome, desferrioxamines). In this context, the team co-directed by Dr. Mislin reports the 3D structures of five outer membrane siderophore transporters (a sixth is under investigation)**(2)(3)**. Since the outer membrane transporter is the first lock to access to the bacterial inner space, these structural data are required for the design of efficient vector mimicking the specific siderophore. The fate of the ferric-siderophore inside the bacteria is very dependent on the siderophore and on the bacteria considered. The elucidation of the iron release compartment (periplasm or cytoplasm) is crucial to determine the antibiotic family being the more efficiently vectorized. The periplasmic or cytoplasmic fate of all siderophore mentioned above has been thus elucidated by the MMBCA team. More than 50% of articles written on the topic were results of collaboration with other teams and *ca* 30% with foreign scientific institutions (mainly in Europe), highlighting therefore the capacity of Dr Mislin and his team to collaborate easily and fruitfully with different partners.

These fundamental researches led to the design and the synthesis of innovative siderophore based Trojan horse strategy. As an example, in 2015, our group was the first to describe vectorized oxazolidinones antibiotics active against *P. aeruginosa*, although this family of antibiotics is usually active only on Gram-positive pathogens **(4)(5)**. This strategy was further improved for oxazolidinones and used to broaden the spectrum of daptomycin by US competitors. The contributions of Dr Mislin to the siderophore based Trojan horse strategy is recognized and he is amongst the four most cited scientists in this field (with Pr Elizabeth Nolan, MIT, USA; Pr. Marvin Miller, Notre Dame University, USA and Pr Mark Brönstrup, HZI Brauschweig, Germany). This international recognition is illustrated by invited reviews or viewpoint **(1)(6)** but also by invitations to give lectures in prestigious international congresses of medicinal chemistry and microbiology (ex. EFMC-ISMC 2016, ECCMID 2019). Moreover Dr. Mislin and Dr Schalk were both involved in two European grants from the *Innovative Medicines Initiative* (ND4BB translocation, ND4BB enable, 2012-2018) to evaluate the potential of Trojan horse strategy.

Even the Trojan horse strategy was often considered as a pure academic "hobby-horse", very recently cefiderocol (Fetcroja®), the first Trojan horse siderophore conjugate, was approved (US, EU) for treating complex urinary infections in human. This achievement proved the high potential of using siderophore as vectors and settle this strategy in the medicinal chemistry landscape. Academic scientists should support this booming field by investigating the new therapeutic perspectives offered by the siderophore vectorization. In the last four years Dr.

Mislin applies his knowledge in bacterial iron-uptake systems and his skills in siderophore vectors synthesis to expand the application of the Trojan horse strategy by using his impressive siderophore toolbox for the vectorization of unusual antibacterial compounds. In this context, Dr. Mislin was granted to investigate the vectorization of metallic photosensitizers in pathogenic bacteria to develop targeted antibacterial dynamic phototherapy **(7)**. In the frame of several ongoing projects, the vectorization of nucleic acid and nucleic acid mimics was envisaged. The proposal of Mr Resende is part of this new scientific challenge.

Along with the increase of antibiotic penetration, the high affinity (nM range) of the ferric-siderophore for its specific membrane transporters can also be used to improve the interaction between macromolecular systems and bacterial membranes. Dr Mislin was recently granted to develop unprecedented siderophore-targeted microbubbles useable for sonobactericide (use of ultrasound and microbubbles cavitation to kill bacteria and destabilize biofilms). A proof of concept of this targeted sonobactericide was recently obtained in the frame of a collaboration with the Erasmus Medical Center in Rotterdam (NL) using vancomycine-targeted microbubbles against *S. aureus* biofilms **(8)**. Drug delivery using siderophore-targeted liposomes is also under investigation in the MMBCA team in the frame of a project starting in October 2023.

References :

(1) Schalk IJ, **Mislin GLA**. Bacterial Iron Uptake Pathways: Gates for the Import of Bactericide Compounds. *J. Med. Chem.* **2017**, *60*, 4573-4576.

(2) Moynié L, Milenkovic S, **Mislin GLA**, Gasser V, Malloci G, Baco E, McCaughan RP, Page MGP, Schalk IJ, Ceccarelli M, Naismith JH. The complex of ferric-enterobactin with its transporter from *Pseudomonas aeruginosa* suggests a two-site model. *Nat. Commun.* **2019**, *10*, 3673.

(3) Normant V, Josts I, Kuhn L, Perraud Q, Fritsch S, Hammann P, **Mislin GLA**, Tidow H, Schalk IJ. Nocardamine-Dependent Iron Uptake in Pseudomonas aeruginosa: Exclusive Involvement of the FoxA Outer Membrane Transporter. *ACS Chem. Biol.* **2020**, *15*, 2741.

(4) Paulen A, Gasser V, Hoegy F, Perraud Q, Pesset B, Schalk IJ, **Mislin GLA**. Synthesis and antibiotic activity of oxazolidinone-catechol conjugates against *Pseudomonas aeruginosa*. *Org. Biomol. Chem.* **2015**, *13*, 11567.

(5) Moynié L, Hoegy F, Milenkovic S, Munier M, Paulen A, Gasser V, Faucon AL, Zill N, Naismith JH, Ceccarelli M, Schalk IJ, **Mislin GLA**. Hijacking of the Enterobactin Pathway by a Synthetic Catechol Vector Designed for Oxazolidinone Antibiotic Delivery in *Pseudomonas aeruginosa*. *ACS Infect. Dis.* **2022**, *8*, 1894.

(6) **Mislin GLA**, Schalk IJ.Siderophore-dependent iron uptake systems as gates for antibiotic Trojan horse strategies against *Pseudomonas aeruginosa*. *Metallomics* **2014** ,*6*, 408.

(7) Sauvageot E, Elie M, Gaillard S, Daniellou R, Fechter P, Schalk IJ, Gasser V, Renaud JL, **Mislin GLA.** Antipseudomonal activity enhancement of luminescent iridium(III) dipyridylamine complexes under visible blue light. *Metallomics* **2017**, *9*, 1820.

(8) Kouijzer JJP, Lattwein KR, Beekers I, Langeveld SAG, Leon-Grooters M, Strub JM, Oliva E, **Mislin GLA**, de Jong N, van der Steen AFW, Klibanov AL, van Wamel WJB, Kooiman

K. Vancomycin-decorated microbubbles as a theranostic agent for *Staphylococcus aureus* biofilms. *Int. J. Pharm.* **2021**, 609, 121154.